The Oncologist®

Commentary

Establishing a Standard of Care for Small Bowel Adenocarcinomas: Challenges and Lessons Learned

THORVARDUR R. HALFDANARSON,[a,b] AXEL GROTHEY[c]

[a]Department of Internal Medicine, Division of Hematology, Oncology and Blood & Marrow Transplantation, University of Iowa Hospitals and Clinics, Iowa City, Iowa, USA; [b]Iowa City VA Medical Center, Iowa City, Iowa, USA; [c]Division of Medical Oncology, Mayo Clinic Rochester, Rochester, Minnesota, USA

Disclosures: Axel Grothey: Bayer, Genentech, Regeneron (C/A); Bayer, Daiichi, Imclone, Genentech (RF). The other author indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

Small bowel adenocarcinoma (SBA) accounts for approximately one third of all small intestinal malignancies, with the other major tumor types being neuroendocrine carcinoma, sarcoma, and lymphoma [1]. Risk factors for the development of SBAs are incompletely understood, but there appears to be an association between SBA and colorectal carcinoma, suggesting that these two malignancies may share a common pathogenesis [2]. The risk of SBA is also increased in patients with inflammatory bowel disease and hereditary colorectal cancer syndromes [3, 4]. SBA is surprisingly rare given that the small bowel comprises 90% of the intestinal length and 98% of the intestinal surface. Because of its rarity, the biology and natural courses of SBA are not as well explained as for colorectal carcinoma and esophagogastric cancers [5].

Recent studies have suggested a closer resemblance of SBA to colorectal carcinoma than to upper gastrointestinal malignancies [6, 7]. However, despite the resemblance, SBA appears to have an inferior stage-adjusted prognosis when compared to colorectal carcinoma [8]. There appears to be a slight increase in the incidence of SBA over recent years, especially duodenal adenocarcinoma, which may in part be explained by increasing use of upper endoscopies [1]. Most SBAs arise in the duodenum, and patients with duodenal SBA appear to have worse prognoses than patients with jejunal or ileal SBA according to some studies [1]. The reason for the inferior prognosis of duodenal SBA is unexplained, but may partly be secondary to understaging and incomplete lymph node sampling at the time of surgery [6]. Given the fact that almost one third of patients presents with metastatic disease and because many patients with earlier stage disease are not candidates for curative resection or suffer relapse following surgery, there is a great need for improving the treatment options for patients with advanced SBA [1, 9].

Due to the relative rarity of SBA, prospective trials limited to this disease are few and the optimal therapy for advanced SBA as well as resected node-positive SBA is unknown. Retrospective studies indicate that chemotherapy can improve the survival of patients with metastatic SBA compared to no treatment [10]. To date, no prospective trials have been performed to demonstrate a survival benefit of chemotherapy and it is very unlikely that such studies will ever be done. Few prospective single-arm studies have been completed in advanced SBA. An Eastern Cooperative Oncology Group study of 5-fluorouracil, doxorubicin and mitomycin C yielded discouraging results, with a low response rate of 18% and substantial toxicities [11]. Two small prospective phase II trials evaluated the combination of a fluoropyrimidine and oxaliplatin and found it to be both effective and well tolerated [12, 13]. The efficacy of a fluoropyrimidine-oxaliplatin combination is further supported by two retrospective studies, suggesting this regimen is both safe and feasible in practice [14, 15].

In situations for which there is paucity of randomized trials, well-performed retrospective studies can provide very valuable information to guide treatment decisions. Tsushima et al. [16] are to be commended for performing such a study. In their retrospective multicenter study, the survival of patients with advanced SBA receiving first-line therapy was compared among five different treatment groups. While there was some

Correspondence: Axel Grothey, M.D., Division of Medical Oncology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Telephone: +1-507-284-4430; Fax: +1-507-284-1803; e-mail: grothey.axel@mayo.edu Received July 30, 2012; accepted for publication July 31, 2012; first published online in *The Oncologist Express* on August 24, 2012. 1083-7159/2012/$20.00/0 http://dx.doi.org/10.1634/theoncologist.2012-0323

heterogeneity between the patients of each group, the combination of fluoropyrimidine and oxaliplatin produced the longest progression-free and overall survival, even after adjusting for relevant prognostic factors. These findings are not surprising given the purported similarities between SBA and colorectal carcinoma and the results of the previously reported phase II trials. It is unclear if the outcome of patients with advanced SBA is inferior to colorectal cancer when treated with the same chemotherapy regimen because data on SBA are much more limited and the use of postprogression therapy is likely more limited.

Two recent studies in SBA using a fluoropyrimidine plus oxaliplatin combination—a phase II trial and a retrospective multicenter study—reported overall survival in the range of what is to be expected in metastatic colorectal cancer [12, 15]. These findings are in line with the observation of Tsushima et al. [16]. The location of the primary tumor may also affect prognosis. Patients with duodenal SBA have consistently been reported to have inferior survival to those with nonduodenal primaries, but data on outcomes in the metastatic setting are very limited. Two recent studies indicated that there was little difference in survival among patients with metastatic duodenal versus nonduodenal SBA [10, 15]. There is a possibility that some patients with cancer of the ampulla of Vater may have been misclassified as duodenal SBA, but ampullary cancer is commonly considered to be of biliary origin and as such, generally treated with gemcitabine-based regimens. The role of targeted agents routinely used in the treatment of colorectal carcinoma such as cetuximab and bevacizumab is unknown, but the use of both agents has been reported in individual patients and further evaluation is warranted [17, 18].

There is clearly an unmet need for larger randomized trials aimed at patients with SBAs, but the rarity of this malignancy makes such efforts daunting. For such a trial to be successfully completed, a concerted and international effort is desirable, preferably across several cooperative groups. The International Rare Cancers Initiative is a recently formed initiative in which the European Organization for Research and Treatment of Cancer, the U.S. National Cancer Institute, Cancer Research UK, and the National Institute for Health Research Cancer Research Network have joined forces to design and fund clinical trials in rare cancers. One of the key initiatives of the International Rare Cancers Initiative is to launch an international treatment trial in metastatic SBA. It is crucial that future SBA trials include an effort to further elucidate the biology of SBA and how best to incorporate novel therapeutic agents.

Until the results of larger trials become available, the combination of a fluoropyrimidine, such as 5-fluorouracil or capecitabine, and oxaliplatin remains a very reasonable first line chemotherapy for metastatic SBA.

Author Contributions

Conception/Design: Axel Grothey
Manuscript writing: Thorvardur R. Halfdanarson, Axel Grothey
Final approval of manuscript: Thorvardur R. Halfdanarson, Axel Grothey

References

1. Bilimoria KY, Bentrem DJ, Wayne JD et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009;249:63–71.

2. Delaunoit T, Neczyporenko F, Limburg PJ, Erlichman C. Pathogenesis and risk factors of small bowel adenocarcinoma: a colorectal cancer sibling? Am J Gastroenterol 2005;100:703–710.

3. Shaukat A, Virnig DJ, Howard D et al. Crohn's disease and small bowel adenocarcinoma: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2011;20:1120–1123.

4. Koornstra JJ, Kleibeuker JH, Vasen HF. Small-bowel cancer in Lynch syndrome: Is it time for surveillance? Lancet Oncol 2008;9:901–905.

5. Zhang MQ, Chen ZM, Wang HL. Immunohistochemical investigation of tumorigenic pathways in small intestinal adenocarcinoma: A comparison with colorectal adenocarcinoma. Mod Pathol 2006;19:573–580.

6. Overman MJ, Pozadzides J, Kopetz S et al. Immunophenotype and molecular characterisation of adenocarcinoma of the small intestine. Br J Cancer 2010;102:144–150.

7. Haan JC, Buffart TE, Eijk PP et al. Small bowel adenocarcinoma copy number profiles are more closely related to colorectal than to gastric cancers. Ann Oncol 2012;23:367–374.

8. Overman MJ, Hu CY, Kopetz S et al. A population-based comparison of adenocarcinoma of the large and small intestine: Insights into a rare disease. Ann Surg Oncol 2012;19:1439–1445.

9. Howe JR, Karnell LH, Menck HR, Scott-Conner C. The American College of Surgeons Commission on Cancer and the American Cancer Society. Adenocarcinoma of the small bowel: Review of the National Cancer Data Base, 1985–1995. Cancer 1999;86:2693–2706.

10. Halfdanarson TR, McWilliams RR, Donohue JH, Quevedo JF. A single-institution experience with 491 cases of small bowel adenocarcinoma. Am J Surg 2010;199:797–803.

11. Gibson MK, Holcroft CA, Kvols LK, Haller D. Phase II study of 5-fluorouracil, doxorubicin, and mitomycin C for metastatic small bowel adenocarcinoma. ***The Oncologist*** 2005;10:132–137.

12. Overman MJ, Varadhachary GR, Kopetz S et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of vater. J Clin Oncol 2009.

13. Xiang XJ, Liu YW, Zhang L et al. A phase II study of modified FOLFOX as first-line chemotherapy in advanced small bowel adenocarcinoma. Anticancer Drugs 2012;23:561–566.

14. Overman MJ, Kopetz S, Wen S et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer 2008;113:2038–2045.

15. Zaanan A, Costes L, Gauthier M et al. Chemotherapy of advanced small-bowel adenocarcinoma: A multicenter AGEO study. Ann Oncol 2010;21:1786–1793.

16. Tsushima T, Taguri M, Honma Y et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. ***The Oncologist*** 2012;17:1163–1170.

17. Tsang H, Yau T, Khong PL, Epstein RJ. Bevacizumab-based therapy for advanced small bowel adenocarcinoma. Gut 2008;57:1631–1632.

18. Santini D, Fratto ME, Spoto C et al. Cetuximab in small bowel adenocarcinoma: A new friend? Br J Cancer 2010;103:1305.

See the accompanying article on pages 1163–1170 of this issue.